SUMMARY MINUTES

OF THE

IMMUNOLOGY DEVICES PANEL MEETING

September 19, 1997

OPEN SESSION

Conference Rooms D and E
5600 Fishers Lane
Rockville, MD

Immunology Devices Panel Meeting

September 19, 1997

Attendees

Charles T. Ladoulis, M.D.
Chairperson

Peter Maxim, Ph.D.
Executive Secretary

Panel Members

Worta J. McCaskill-Stevens, M.D.

Gustavo Reynoso, M.D.

Mary M. Kemeny, M.D.

Sheila E. Taube, Ph.D.

Henry A. Homburger, M.D.

Glen L. Hortin, M.D., Ph.D.

Industry Representative

Erika B. Ammirati, R.A.C.

Consumer Representative
Wilbert C. Jordan, M.D., M.P.H.

FDA Representatives

Steven I. Gutman, M.D., M.B.A.
Arleen Pinkos, MT (ASCP)

OPENING REMARKS-INTRODUCTIONS

Executive Secretary Peter Maxim, Ph.D., opened the meeting at 10:00 a.m. and welcomed panelists and participants. He read the conflict of interest statement, and noted that Glen L. Hortin, M.D., Ph.D., had been cleared to participate in the meeting. Chairperson Charles T. Ladoulis, M.D., introduced FDA's presentation of its new initiatives for product reviews. The new protocols promise to facilitate and promote expeditious reviews. They will also address the difficulties in reviewing submissions and will benefit the agency, he said.

FDA PRESENTATIONS

Product Development Protocol (PDP)

Interim Chief, Microbiology Branch, Arleen Pinkos, MT (ASCP) briefly described the PDP as a new initiative being proposed as part of FDA's re-engineering efforts. It provides manufacturers of Class III devices an alternative to the premarket approval (PMA) process and may reduce the resources and time required to review such devices. She stressed, however, that the safety and effectiveness requirements for PDPs will be comparable to those for the PMAs.

After describing how a device normally reaches the market, she showed how the PDP program involves FDA much earlier in the review process. Ms. Pinkos said the advisory panels will be asked to review and comment on the protocol and proposed acceptance criteria, instead of the data and study conclusions. FDA will make a decision for approval or disapproval within 120 days of receiving submissions filed under the PDP. She then described each stage in the

PDP process: presubmission, filing review, FDA review, preclinical phase, clinical phase, modifications to PDP, notice of completion, and completion. According to Ms. Pinkos, the PDP will eventually assist the rapid development of innovative devices, because it should be less extensive than the conventional two-step investigation and PMA process. For more information, interested persons can call Dr. Lillian Yin, contact the Center's Web site, or attend a PDP workshop scheduled for October 22.

Ms. Pinkos and Steven I. Gutman, M.D., M.B.A., discussed issues of intended use and thresholds of performance with panel members. She stressed that the new emphasis is on "what is going to happen." Dr. Jordan is excited about PDP, but noted that there will be greater responsibility at FDA and reviewers will require lots of expertise. Sheila E. Taube, Ph.D., acknowledged that working early on with manufacturers is a good idea. However, it is not always possible to predict the outcome, she said. Ms. Pinkos again explained the advantages of the PDP and said that manufacturers and FDA will agree to protocols and endpoints before the protocol is begun. The possibility that outcomes will not be achieved is always present.

Discussion continued. Dr. Maxim reminded panelists that the PDP is being developed as a highly interactive process. Ms. Pinkos said that terms can be renegotiated during the process. Dr. Ladoulis concluded the discussion noting the process will be better for the industry and in the public interest.

New 510(k) Paradigm

Dr. Gutman said FDA is re-engineering the workload, by decreasing the FDA review of low-risk devices in Classes I and II. He described the new 510(k) paradigm's three-step process: The first step requires FDA to revisit and update the classification system (identify Class I devices that are low-risk products with well-established technologies). The second step involves enhanced CGMP requirements. The third step is characterized as an abbreviated 510(k) where FDA identifies the standards that manufacturers follow. Dr. Gutman then distinguished between Class I and Class I exempt devices, and listed references used for developing standards (NCCLS, the Chemistry Branch, monographs from professional groups, such as AACC, and from ISO-IFO).

First Year of Tumor Marker Reclassification

Dr. Maxim described the rationale for and outcome of the petition to reclassify tumor markers from Class III to Class II devices that only require the 510(k) process but with special controls. The time to achieve the reclassification, first thought to be 18 - 24 months, was actually 9 months, he said. Thirty 510 (k)s have been reviewed this past year, 13 were found to be substantially equivalent, and the review times averaged approximately 125 days.

According to Dr. Maxim, key components of the draft guidance document include the administrative requirements for nonclinical laboratory studies, and for clinical studies. He then discussed methods for displaying substantial equivalence and for presenting performance

characteristics with comparison devices and asked the panel to consider several issues during their afternoon deliberations.

OPEN PUBLIC HEARING

Health Industry Manufacturers Association (HIMA)

Representative Ms. Carolyn Jones commended FDA for its speed in reclassifying tumor markers. She claimed, however, that the agency is not following its own guidance document when it requires clinical studies in a target patient population for "me-too" markers. She said FDA provides no basis for the studies, which are of only questionable benefit and have practical limitations that impact the utility of the findings. HIMA recommends that FDA follow the published guidance document and not require the clinical studies.

Centocor, Inc.

Mr. Christopher Zalesky echoed Ms. Jones comments. He then stated that the reclassification has been successful, the guidance document is adequate, and the target patient clinical studies have limited scientific and regulatory value. He listed several issues to discuss and recommended that FDA explore the use of well-characterized serum pools or rely more heavily on the literature.

American Association of Clinical Chemistry (AACC)

After describing the AACC, Dr. Daniel Chan stated its strong support of FDA's

reclassification of tumor markers. The association also supports the guidance document and encourages manufacturers to provide sufficient scientific and clinical information (as outlined in the document) to prove the substantial equivalence of their markers.

Dr. Chan and Dr. Ladoulis discussed the need to demonstrate satisfactory device performance characteristics. Dr. Chan contended that the manufacturer should also prove safety and efficacy on a target patient population.

OPEN COMMITTEE DISCUSSION

Dr. Maxim asked the panel to consider the data requirements for Class II tumor markers considering three scenarios: (1) well known tumor markers with several approvals such as CEA, AFP, and PSA; (2) CA 27.29, CA 15-3, markers that the agency has better experience with and (3) CA-125 which has an extensive literature base but no approvals. The responses were varied. Worta J. McCaskill-Stevens, M.D., noted that the burden was greater for the applicant on the primary approval. There is also a concern of interference of new drug treatments as more experience is gained with the marker and new drugs are added to treatment requirements. Dr. Ladoulis is concerned about the claims—whether the tumor markers approved for disease monitoring or diagnostic screening, as with PSA. Sheila E. Taube, Ph.D., said the side-by-side comparison methodology is useful. Regarding drug interactions, she asked if testing in some stored "spiked" samples would be valid. Gustavo Reynoso, M.D., recommended following serially the same patient when doing a "me-too" test to take into account the changes over time

in the same individual and to show clinical parallelism. Erika B. Ammirati, R.A.C., noted the difficulties in finding fresh samples and recommended *in vitro* interference testing using introduced metabolites in reference samples.

Dr. Hortin said it would be more appropriate to stratify the markers according to response to risk and clinical impact. Mary M. Kemeny, M.D. said good ethnic diversity is often lacking and there are difficulties in obtaining large numbers of breast cancer patients. According to Henry Homburger, M.D., "you don't need clinical studies unless you change the clinical measurements." Further, he said with highly heterogenous markers and multiple antigenic sites and measures, the metabolic fate is unknown. He recommends stratification of data requirements according to immunochemistry and metabolic behavior.

According to Dr. Reynoso, there is a need for stratification, because not all tests are judged the same. Analytical equivalence may be okay for some tests, he said.

Panelists then discussed the role of patents, the effect of requiring substantial equivalence for me-too products, and the fairness of the guidance document. Dr. Maxim said FDA is currently holding all manufacturers to a high level of proof and the requirements are not inconsistent with the guidance. Dr. Gutman said FDA is looking for minimum thresholds. Wilbert C. Jordan, MD., M.P.H., said "me-too" devices should have no less than a 95% specificity and sensitivity; high-risk devices should be at 99%. Dr. Kemeny said "me-too"

devices may be more sensitive if the first is considered the gold standard. Dr. Ladoulis said these devices need to be tested with fresh samples for short-term serial study in a target population to ensure performance in same matrix. Interference effects with current drug therapies, not previously used for disease management should also be evaluated during this study. Dr. Taube said showing concordance and then a side-by-side comparison with fresh samples should be sufficient. Discussion ensued on the validation of substantial equivalence in performance versus clinical claims. The problems of conducting clinical studies were noted by Drs. Ammirati and Ladoulis. Dr. Reynoso said there is a point when clinical utility does not need to be reviewed. FDA can define the analytical data (based on the biochemistry and similarities between the antibody and antigen) sufficient for product clearance, he added. Panelists then debated the use of serum banks (Dr. Homburger raised the issue of using rigorously maintained serum banks instead of following patients for 3 to 5 years; Dr. Taube recounted the problems that caused the National Cancer Institute to close its bank after 20 years.)

Drs. Taube and Ladoulis agreed that recruiting patients for tests is difficult. Panelists discussed definitions of degree of comparability and substantial equivalence, clinically useful cut- offs, and the need to measure specificity and sensitivity. Dr. Homburger noted the balancing act manufacturers face: the more they know about what they are testing, the less they need to perform clinical studies. He said the requirements for obtaining clinical data are inversely proportional to the analytical characterization of the test.

Dr. Reynoso said patient studies will be needed in some cases, but not in others. Dr. Ladoulis said some clinical evaluation must be done but Dr. Kemeny said in some cases equivalence can be shown without clinical studies. Dr. Reynoso said the guidance document probably should be modified to reflect the day's discussion, and FDA should consider parallel studies over time on the same patient as part of determining equivalence.

A member of the audience, Glen Paul Freiberg, R.A.C., addressed the panel. He said a serum bank is valid for analytes under review and debated with an FDA staff person on the need for additional testing when good correlation exists on one test. Although manufacturers do not need to study every outcome to determine clinical equivalence, they have to show that a patient with disease by one test is also positive with another test, said Dr. Taube.

ADJOURNMENT

The meeting was adjourned at 3:40 p.m.

I certify that I attended the meeting of the Immunology Devices Panel on September 19, 1997, and that these minutes accurately reflect what transpired.

Peter Maxim, Ph.D.
Executive Secretary, FDA

I approve the minutes of this meeting as recorded in this summary.

Charles T. Ladoulis, M.D.
Chairperson

Summary prepared by
Joëlle Lofton
for Elements in Style, Inc.
15065 Joshua Tree Road
North Potomac, MD 20878
301-294-6217